Remarks

Claims 17 and 18 are currently amended. Claims 17, 18, 20, 22-26 and 36-45 are pending. Support for the amendments to the claims is found in the specification. For example, the support for "at least one non-naturally occurring variant monomer of a TNFSF protein" and "at least one a naturally occurring TNFSF monomer of said TNFSF protein" is found in Figure 1. Applicants respectfully submit that this amendment is not new matter. Applicants respectfully submit that the claims, as amended, are in condition for allowance.

Claim Rejections – 35 U.S.C. § 102

Claims 17-20, 23, 33, 36, 38, 40, 41, 44 and 49 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent 6,171,787 (the '787 patent) to Wiley.

The Examiner's position appears to be that the claims read on heterotrimers of TNFSF proteins, where monomers from different types of TNFSF proteins can be included in the heterotrimer. As such, the Examiner reasons, wild type TNF-γ of the '787 patent will exchange *in vivo* with other TNFSF members to form heterotrimers that do not activate receptor signaling.

As a preliminary matter, the Applicants respectfully disagree. There is no evidence to suggest that TNF-γ will exchange with other members of the TNFSF (e.g. non-TNF-γ members of the family) and form heterotrimers with a decrease in receptor activation. In fact, what evidence is available shows that TNFSF members do not exchange with each other to form dominate negative heterotrimers. Attached as Exhibit A is the recent article "Dominant-Negative Inhibitors of Soluble TNF Attenuate Experimental Arthritis without Suppressing Innate Immunity to Infection" by Zalevsky et al., J IMMUNOL. 2007 Aug 1;179(3):1872-83. (Dr. Zalevsky and many of other authors are current or former employees of Xencor, Inc., the assignee of the present application.) As shown in Figure 1 and the first full paragraph of page 1876, TNF-alpha does not exchange with TNF-beta (also called lymphotoxin α,) the most closely related cytokine to TNF-alpha to form dominate-negative heterotrimers. Specifically:

> Because many proteins in the TNF superfamily share conserved structural features, it was important to determine whether the exchange mechanism of DN-TNF is specific for [TNFα]; therefore, a signaling assay was established to measure inhibition of lymphotoxin α [soluble-TNFβ], the most closely related cytokine. As described above, the three classes of TNF inhibitors blocked recombinant mouse solTNF (Fig. 1*B*). However, DN-TNF and [antibody] failed to block recombinant mouse lymphotoxin α (each with a >

> 1000-fold loss of potency relative to solTNF), while the decoy receptor retained activity (Fig. 1*E*), in agreement with a previous report (26). Taken together, the five studies shown in Fig. 1 demonstrate that DN-TNF biologics effectively antagonize recombinant or endogenously produced solTNF with comparable overall efficacy to a decoy receptor and anti-TNF Abs; however, DN-TNF does not block the activity of lymphotoxin α.

Thus, since DN-TNFα does not exchange and block activity of its most closely related cytokine, lymphotoxin α, there is no reason to assume the less related TNF-γ will do so. Applicants respectfully submit that wild-type TNFSF members do not exchange with each other *in vivo* to create dominant-negative heterotrimers, and the rejection under 35 U.S.C. § 102 should be withdrawn.

As discussed during the interview of July 10, 2007, BLyS and APRIL, two members of the TNFSF, appear to exchange to form biologically active heterotrimers. Attached, as Exhibit B, is the article "BLyS and APRIL Form Biologically Active Heterotrimers That Are Expressed in Patients with Systemic Immune-Based Rheumatic Diseases," by Roschke et al., J IMMUNOL. 2002 Oct 15;169(8):4314-21. As the title states, and the results support, any BLyS/APRIL heterotrimers are biologically active, meaning they cause receptor signaling, and are thus outside the scope of the present claims. Again, Applications are not aware of any wild-type TNFSF member which will exchange with any other TNFSF member *in vivo* to form a dominant-negative heterotrimer.

The Office Action cited Col. 2, lines 12-14 teaches "an engineered soluble version of TNF-gamma, as well as cell surface expressed form of TNF-gamma." Applicants respectfully submit that this paragraph teaches the wild-type TNF-gamma that has been "engineered" to express in a host cell. The Office Action also cites the '787 as teaching recombinant polypeptides (col. 11, lines 1-11) and "synthetic peptides" (col. 11, lines 12-15). Applicants respectfully submit that these paragraphs only teach methods of making the wild-type sequence disclosed elsewhere in the '787 patent, and do not teach any variant TNFSF protein. A "synthetic peptide" is merely a peptide made by chemical means – just like "synthetic water" is taking two parts hydrogen gas and mixing it with one part oxygen gas, adding heat to form H_2O. A "synthetic" molecule, a "recombinant" molecule, or a naturally produced and purified molecule will have inherent characteristics regardless of the method of production, as pointed out by the Office Action on page 6 (citing *In re* Papesch and *In re* Von Schickh).

The Office Action in the paragraph bridging pages 6-7 states that the '787 patent discloses synthetic fragments with or without substitutions, which inhibit activation of the TNFSF polypeptide or the

TNFSF receptor, citing col. 4, lines 31-39 and col. 31, lines 66 – col. 32, line 21). Applicants respectfully disagree with this characterization of the '787 patent. The '787 patent does not actually disclose any synthetic peptide sequence. Columns 31-32 merely speculate that one of skill in the art could make peptides that might be used "as agonists and antagonists." However, no where in the '787 patent is there a disclosure of how one would actually make an antagonist, let alone an antagonist which operates by exchanging *in vivo* to form a dominant-negative heterotrimer. Likewise, column 4 broadly states that a "compound which inhibits activation of the TNF-gamma polypeptide is provided." However, Applicants are unable to find any example in the '787 patent where Wiley actually made a TNF-gamma inhibiting compound, or any further teaching on how one of skill in the art could make such a TNF-gamma inhibiting compound. The only sequences taught or suggested in the '787 patent are wild-type sequences, and these do not exchange with other TNFSF sequences to form a heterotrimer with 50% or 90% decreased receptor activation.

The Office Action states, "since inhibitors that bind to soluble TNFSF polypeptides that normally bind to TNFSF receptors are contemplated, the limitations of claims 20 and 44 have been met." Applicants respectfully submit that inhibitors binding to a homotrimer of a TNFSF polypeptide is not the same as a TNFSF variant that exchanges *in vivo* with a wild-type TNFSF polypeptide to form a TNFSF heterotrimer. The sequences disclosed in the '787 patent do not inherently meet the limitations of the pending claims.

As the Examiner is aware, "'the fact that a certain result or characteristic <u>may</u> occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.' *In re* Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art)." MPEP §2112(IV) (emphasis in original). Applicants respectfully submit that nothing in the '787 patent teaches or suggests the present claims, or inherently meet the claim limitations. Since the '787 patent does not inherently teach or suggest the present claims, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

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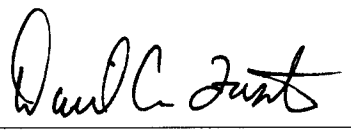
Dated: August 21, 2007 By: 

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